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Ruboxistaurin

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Abstract

Ruboxistaurin, an orally active protein kinase C beta (PKC beta) inhibitor, is a macrocyclic bisindolylmaleimide compound under development by Eli Lilly with potential as a therapy for diabetic macular oedema and other diabetic angiopathies, including diabetic retinopathy, diabetic peripheral neuropathy and diabetic nephropathy.

Ruboxistaurin is awaiting approvals in the US and Europe for the treatment of diabetic retinopathy.

Eli Lilly and Alcon entered into a long-term agreement to co-promote ruboxistaurin in the US and Puerto Rico for diabetic retinopathy. The agreement is subject to the US FDA's approval of the agent for this indication. Under the terms of the agreement, Alcon will assume primary responsibility for promotion to eye specialists including retinal specialists and general ophthalmologists, while Eli Lilly will be targeting endocrinologists and physicians. Subject to approval in the US, Eli Lilly will receive milestone and marketing payments from Alcon. Alcon in turn will receive compensation based on product sales.[1]

In December 2003, Eli Lilly signed a joint development and co-marketing agreement with Takeda Chemical Industries for ruboxistaurin in the Japanese market. Under the terms of the agreement, Eli Lilly Japan and Takeda will jointly develop ruboxistaurin in Japan, will file an NDA for diabetic peripheral neuropathy and diabetic retinopathy, and subsequently will market the drug in Japan.[2]

Ruboxistaurin was submitted for approval in Europe in the second quarter of 2006.[3]

The agent is also in phase II studies for the treatment of diabetic maculopathy (macular retinopathy) in Japan.

Data from a phase III, 3-year study of ruboxistaurin in patients with moderate to severe diabetic retinopathy showed that ruboxistaurin markedly reduced the risk of sustained vision loss compared with placebo. This multicentre, randomised study, named PKC-DRS2 (Protein Kinase C-Diabetic Retinopathy Study 2), was conducted at 70 clinical sites and involved 685 patients with diabetic retinopathy.[4]

The agent is also in a phase II study in the US, Canada and Europe in patients with clinically significant macular oedema. The trial (B7A-MC-MBCU), which will evaluate oral administration of the drug using optical coherence tomography over a period of 18 months, is expected to enrol approximately 220 patients. This randomised, double-blind, placebo-controlled study was initiated in August 2005 and is expected to be completed in March 2008.

Previously, results of the PKC-Diabetic Retinopathy Study (PKC-DRS) showed that ruboxistaurin at a dose of 32 mg/day has potential to reduce the risk of moderate vision loss especially in patients with diabetic macular oedema. This phase III, randomised, double-blind, multidose study in 252 patients with type 1 and type 2 diabetes receiving ruboxistaurin or placebo for 3-4 years evaluated the safety of the agent and its effect on progression of diabetic retinopathy, moderate vision loss and sustained moderate vision loss. The study was conducted at Joslin Diabetes Center and at centres in the US, Canada, Denmark, The Netherlands and the UK.[5]

In 2004, Eli Lilly presented new analysis of previously reported data for ruboxistaurin in diabetic macular oedema indicating that ruboxistaurin has the potential to decrease the progression of diabetic macular oedema involving the center of the macula.[6]

Positive results from the PKC Beta Inhibitor Diabetic Macular Edema (PKC-DMES) trial were reported in 2003.[7]

Eli Lilly expected to file for approval of ruboxistaurin for the treatment of diabetic peripheral neuropathy in the US and Europe in 2005.[8,9] However, no development was reported for this indication.

On 15 March 2007, Eli Lilly withdrew its marketing authorisation application for ruboxistaurin for diabetic retinopathy filed with EMEA in May 2006. Its current development status in the EU is unclear at this stage.

1. Profile

1.1 Pharmacokinetics

The pharmacokinetics and safety of multiple oral doses of ruboxistaurin were assessed in a two-part study in 18 and 8 healthy volunteers, respectively. In part I, volunteers received 8, 16 or 32mg as a single dose then as twice-daily doses for 7 days, whereas in part II, ruboxistaurin 16mg was administered twice daily for 4 weeks. All doses were given after meals. The pharmacokinetics of ruboxistaurin were linear within the dose range and duration of the study. Steady state was achieved after 7–21 days with the twice-daily dosing. Ruboxistaurin given in the evening had lower plasma concentrations and a longer time to maximal concentration compared with the morning dosage.[10,11]

In six patients with end-stage renal disease and a matched group of six healthy volunteers, there were no significant differences in the pharmacokinetics of single doses of 32mg of ruboxistaurin. Chronic haemodialysis procedure required by patients with renal impairment had no effect on elimination of ruboxistaurin. [12]

1.2 Adverse Events

The safety of multiple oral doses of ruboxistaurin were assessed in a two-part study in 18 and 8 healthy volunteers, respectively. In part I, volunteers received 8, 16 or 32mg as a single dose then as twice-daily doses for 7 days, whereas in part II, ruboxistaurin 16mg was administered twice daily for 4 weeks. All doses were given after meals. Ruboxistaurin appeared to be safe and well tolerated at all doses tested.[10,11]

Table I. Features and properties

Chemical name	9(*S*)-9-[(Dimethylamino)methyl]-6,7,10,11-tetrahydro-9*H*,19*H*-5,21:12,17-dimethenodibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecene-18,20-dione
Molecular formula	C28 H28 N4 O3
CAS number	169939-94-0
WHO ATC code	A10X (Other Drugs Used in Diabetes) C01 (Cardiac Therapy) S01X-A (Other ophthalmologicals)
EphMRA ATC code	A10X (Other Drugs Used in Diabetes) C1 (Cardiac Therapy) S1X (Other Ophthalmologicals)
Originator	Eli Lilly: USA
Licensee companies	Takeda: Japan Alcon: Puerto Rico: USA
Highest development phase	Phase No development reported (USA)
Properties	
Mechanism of action	Protein kinase C inhibitors
Pharmacodynamics	Normalises GFR and filtration fraction, reduces urinary albumin excretion, and prevents abnormal retinal enzyme activity in diabetic rats; restores cardiac function in failed murine hearts
Route	Oral
Adverse events	Occasional: Cough, Headache, Hypertension, Nasopharyngitis

Ruboxistaurin 32 mg/day was generally well tolerated as per analysis of the data from the two 30-month and 3-year phase III clinical studies in ≥900 patients with diabetic retinopathy and various degrees of diabetic macular oedema. The most frequently reported adverse events were equally distributed among experimental and placebo groups and included nasopharyngitis, headache, cough and hypertension.[6]

Ruboxistaurin was well tolerated in a 1-year pilot study in 123 patients with type 2 diabetes and diabetic nephropathy. In this multicentre (17 sites in the US), randomised, double-blind, parallel group, placebo-controlled study, the most frequently reported adverse event was hypertension. Three ruboxistaurin recipients withdrew from the study as a result of adverse events (decreased libido, impaired mental status and metastatic cancer).[13]

Safety analysis from 11 studies (phase II and III) of ruboxistaurin 32 mg/day in 2804 patients with at least one diabetic microvascular complication (including diabetec retinopathy) showed ruboxistaurin was generally well tolerated with a similar serious adverse events profile to placebo. Serious adverse events occurred in 23.2% of patients on placebo compared with 20.8% of patients on ruboxistaurin. Ruboxistaurin had no effect on glucose or blood pressure control. The only treatment-related adverse event with a frequency >2% in the ruboxistaurin group was indigestion.[14,15]

1.3 Pharmacodynamics

1.3.1 Diabetes

Preclinical studies: Ruboxistaurin selectively inhibited the protein kinase C β_1 and β_2 isoenzymes with respective IC_{50} values of 4.7 and 5.9 nmol/L *in vitro*. In mice, ruboxistaurin 1 and 10 mg/kg significantly reduced protein kinase C activity in renal glomeruli, and normalised GFR and filtration fraction. Ruboxistaurin 10 mg/kg for 8 weeks significantly reduced urinary albumin excretion in diabetic rats.[16]

Diabetes results in reduced activity of Na,K-ATPase in the retina; in other tissues, this activity is in turn regulated partially by protein kinase C (PKC) activity. Abnormal PKC activity in the retina of

Table II. Drug development history

Jun 1996	Preclinical development for Diabetic angiopathies in the US (Unknown route)
Sep 1996	Preclinical development for Diabetic retinopathy in the US (PO)
Sep 1996	Phase-I for Diabetic angiopathies in the EU (Unknown route)
Aug 1997	Phase-II for Diabetic nephropathies in the US (Unknown route)
Mar 1998	Preclinical development for Heart failure in the US (Unknown route)
Jun 1998	Phase-I for Diabetic angiopathies in the US (Unknown route)
Jun 1998	Phase-I for Diabetic retinopathy in Europe (PO)
Jul 1999	Phase-III in Diabetic macular oedema in the US (PO)
Jun 2002	Phase-II/III in Diabetic neuropathies in the US (PO)
Aug 2002	No development reported – Phase-II for Diabetic nephropathies in the US (PO)
Aug 2002	No development reported – Preclinical for Heart failure in the US (unspecified route)
Nov 2002	Phase-III in Diabetic retinopathy in the US (PO)
Nov 2002	Phase-III in Diabetic neuropathies in the US (PO)
Dec 2002	Two phase III trials have been completed in diabetic retinopathy and diabetic macular oedema
Jan 2004	Eli Lilly and Takeda have formed a joint development and co-marketing agreement for ruboxistaurin mesylate in Japan
Jan 2004	Phase-II in Diabetic retinopathy in Japan (PO)
Feb 2004	Phase-III in Diabetic macular oedema in Canada (PO)
Feb 2004	Phase-III in Diabetic macular oedema in Europe (PO)
Feb 2004	Phase-III in Diabetic macular oedema in Australia (PO)
Feb 2004	Phase-III in Diabetic macular oedema in Mexico (PO)
Feb 2004	Phase-III in Diabetic macular oedema in Taiwan (PO)
Feb 2004	Phase-III in Diabetic macular oedema in Brazil (PO)
Feb 2004	Phase-III in Diabetic macular oedema in India (PO)
Dec 2004	Clinical trials in Diabetic nephropathies in the US (PO)
Aug 2005	No development reported – Phase-III for Diabetic neuropathies in the US (PO)
Aug 2005	Eli Lilly has completed a phase III trial in diabetic retinopathy and two phase III trials in diabetic peripheral neuropathies in the US
Feb 2006	Preregistration for Diabetic retinopathy in the US (PO)
Apr 2006	Ruboxistaurin has received priority review status for Diabetic retinopathy in the US
Jul 2006	Eli Lilly and Alcon agree to co-promote ruboxistaurin in the US and Puerto Rico for diabetic retinopathy. The agreement is subject to US FDA approval of ruboxistaurin
Jul 2006	Preregistration for Diabetic retinopathy in Europe (PO)
Jul 2006	Eli Lilly and Alcon have entered into an agreement to co-promote ruboxistaurin in US and Puerto Rico for Diabetic retinopathy
Aug 2006	Eli Lilly has received an approvable letter from the FDA for ruboxistaurin in diabetic retinopathy
Oct 2006	The FDA has requested an additional 3-year phase III clinical trial for ruboxistaurin in diabetic retinopathy
Oct 2006	No development reported – Phase-II for Diabetic nephropathies in the US (PO)
Oct 2006	Eli Lilly to appeal the FDA's decision on diabetic retinopathy approval
Mar 2007	Eli Lilly withdraw its marketing authorisation application for ruboxistaurin for diabetic retinopathy filed with EMEA in May 2006. Its current development status in the EU is unclear at this stage

streptozocin-induced diabetic rats was prevented by the administration of ruboxistaurin (10 mg/kg for 2 months). Na,K-ATPase activity was also significantly normalised in treated rats compared with untreated diabetic rats. Ruboxistaurin treatment did not appear to have any effects on glycated haemoglobin levels or bodyweight.[17]

Ischaemia-induced preretinal and optic nerve head neovascularisation was significantly inhibited after oral treatment with ruboxistaurin in a porcine animal model of neovascularisation from branch retinal vein occlusion. Animals received oral ruboxistaurin 1 mg/kg twice daily for 12 weeks after retinal vein occlusion.[18]

1.3.2 Eye Disorders

Diabetic retinopathy: A randomised, double-blind, month-long study in 29 patients with type 1 and type 2 diabetes mellitus assessed the efficacy of multiple oral doses of ruboxistaurin on retinal blood flow and retinal circulation time. Ruboxistaurin 16 or 32 mg/day orally once or twice for 28 days improved retinal blood flow and circulation time compared with placebo, and had no significant effects on blood glucose levels. Ruboxistaurin was safe and well tolerated.[19,20]

1.3.3 Heart Failure

Preclinical studies: Ruboxistaurin selectively inhibited the protein kinase C β_1 and β_2 isoenzymes with respective IC_{50} values of 4.7 and 5.9 nmol/L *in vitro*.[16]

In failed murine hearts, ruboxistaurin reduced total activity of protein kinase C-β by 25%. As a result, hypertrophy was reduced and cardiac function was restored. In a concentration-dependent manner, ruboxistaurin inhibited tissue plasminogen activator and prostaglandin F1-α production in cardiomyocytes and endothelial cells.[21]

1.4 Therapeutic Trials

1.4.1 Diabetes

Diabetic neuropathy: In a randomised, double-blind, parallel, comparative, phase III study in 83 patients with symptomatic diabetic peripheral neuropathies, ruboxistaurin 64 mg/day improved Neuropathy Total Symptom Scores (NTSS).

When the entire cohort was considered, changes in vibration detection threshold did not differ significantly between treatment groups. However, in a subset of 49 patients with early disease, ruboxistaurin 32 and 64 mg/day was associated with significant decreases in vibration detection threshold compared with placebo (1.54 vs 0.24; and 1.10 vs 0.24, respectively). In this group of patients, the change in vibration detection threshold was significantly correlated with the improvement in NTSS-6 score.[22]

The effects of ruboxistaurin 32mg or 64mg for 1 year on diabetic peripheral neuropathy were evaluated in a randomised, double-blind, parallel-group phase II study in a total of 205 patients with type 1 or type 2 diabetes and diabetic peripheral neuropathy. Neurological examination was conducted using the Neuropathy Impairment Score (NIS), including subscores for the lower limbs and reflexes. An improvement in overall NIS, relative to baseline, was observed in patients treated with the 32mg dose of ruboxistaurin, although the difference from the placebo group was not statistically significant. A more marked effect was noted in the lower limb and reflex NIS subscores (both $p < 0.05$ vs placebo). The composite scores of NIS plus electrophysiological and sensory tests were also improved after treatment with ruboxistaurin 32mg. There were no significant differences in NIS or composite scores between the ruboxistaurin 64mg and placebo groups.[23-26]

Analyses from prior study data showed that patients with diabetic peripheral neuropathy (DPN) who took ruboxistaurin experienced relief of a broad range of symptoms of DPN independent of the si-

multaneous use of pain palliative oral medications.[27]

In the 36-month, multicentre, double-blind, placebo-controlled (PKC-DRS) study in 252 patients with moderately severe to very severe nonproliferative diabetic retinopathy, ruboxistaurin had no significant effect on the progression of the disease. Ruboxistaurin, however, demonstrated a trend towards a reduction in the occurrence of moderate visual loss, defined as a doubling of visual angle (from 20/20 vision to 20/40 vision) by 35%.[15,28-30]

Ruboxistaurin 32 mg/day significantly improved visual acuity as per analysis of the data from the two 30-month and 3-year phase III clinical studies in ≥900 patients with diabetic retinopathy and various degrees of diabetic macular oedema. Patients with eyes with diabetic macular oedema involving the centre of the macula significantly improved their visual acuity after ruboxistaurin compared with placebo recipients (71 letter correct vs 60 letters, respectively). The difference was not observed with lower doses of ruboxistaurin.[6]

1.4.2 Eye Disorders

Diabetic retinopathy: Combined analysis from the PKC-DRS and PKC-DRS2 phase III studies demonstrated ruboxistaurin reduced the risk of sustained moderate vision loss by 41% over 3 years when compared with placebo in 813 patients with moderate to severe nonproliferative diabetic retinopathy. Vision loss occurred in only 6.1% of patients treated with ruboxistaurin compared with 10.2% of patients on placebo. The two randomised studies were double-blinded and placebo-controlled.[14]

In the 36-month, multicentre, double-blind, placebo-controlled (PKC-DRS) study in 252 patients with moderately severe to very severe nonproliferative diabetic retinopathy, ruboxistaurin had no significant effect on the progression of the disease. Ruboxistaurin, however, demonstrated a trend towards a reduction in the occurrence of moderate visual loss, defined as a doubling of visual angle (from 20/20 vision to 20/40 vision) by 35%.[15,28-30]

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